(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 291 343 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
12.03.2003 Bulletin 2003/11

(21) Application number: **01941061.2**

(22) Date of filing: **15.06.2001**

(51) Int Cl.[7]: **C07D 213/74**, C07D 401/12, C07D 405/12, C07D 417/12, C07D 409/12, C07D 473/08, A61K 31/44, A61K 31/4439, A61K 31/4545, A61K 31/5377, A61K 31/443, A61K 31/4436, A61K 31/4433, A61K 31/444, A61K 31/522, A61P 13/12, A61P 9/00, A61P 9/10

(86) International application number:
PCT/JP01/05108

(87) International publication number:
WO 01/096309 (20.12.2001 Gazette 2001/51)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

(30) Priority: **15.06.2000 JP 2000180477**
15.06.2000 JP 2000180479
02.11.2000 JP 2000336140
27.11.2000 JP 2000359781

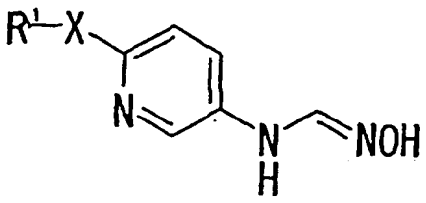
(71) Applicant: **TAISHO PHARMACEUTICAL CO., LTD**
Tokyo 170-8633 (JP)

(72) Inventors:
- **SATO, Masakazu**
  Toshima-ku Tokyo 170-8633 (JP)
- **MIYATA, Noriyuki**
  Toshima-ku Tokyo 170-8633 (JP)
- **ISHII, Takaaki**
  Toshima-ku Tokyo 170-8633 (JP)
- **KOBAYASHI, Yuko**
  Toshima-ku Tokyo 170-8633 (JP)
- **AMADA, Hideaki**
  Toshima-ku Tokyo 170-8633 (JP)

(74) Representative: **HOFFMANN - EITLE**
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München (DE)

(54) **HYDROXYFORMAMIDINE DERIVATIVES AND MEDICINES CONTAINING THE SAME**

(57) Pharmaceutical agents for inhibiting the production of 20-HETE which participates in constriction or dilation of microvessels in major organs such as the kidneys and the cerebral blood vessels, or participates in causing cell proliferation are provided. The present invention relates to hydroxyamidine compounds represented by the formula:



wherein R^1 represents a group represented by the formula: R^2-$(CH_2)_m$- (wherein R^2 represents a C_{3-8} cycloalkyl group, a C_{2-6} alkoxycarbonyl group, a C_{2-10} alkenyl group, a C_{2-6} alkynyl group, a substituted or non-substituted aryl group,

EP 1 291 343 A1

or the like, and m is an integer of 1 to 8), a group represented by the formula: R^3-A- (wherein R^3 represents a hydrogen atom, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, or the like, and A represents a straight-chain C_{2-10} alkylene group which may be substituted with a C_{1-6} alkyl group or a trifluoromethyl group), or a C_{3-8} cycloalkyl group, and X represents an oxygen atom or a sulfur atom,
or pharmaceutically acceptable salts thereof, and relates to medicines including the same as active ingredients.

Description

Technical Field

[0001] The present invention relates to hydroxyformamidinopyridine derivatives inhibiting a synthase of 20-hydroxyeicosatetraenoic acid (20-HETE) biosynthesized from arachidonic acid.

Background Art

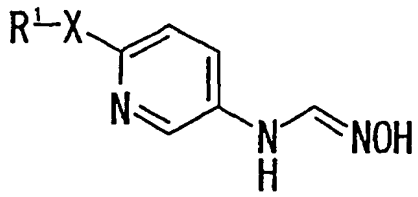
[0002] Prostaglandins produced by cyclooxygenase and leucotrienes produced by lipoxygenase have been well known as physiologically active substances synthesized from arachidonic acid. Recently, it has been elucidated that 20-HETE, which is produced from arachidonic acid by the cytochrome P450 family enzymes, functions in various manner *in vivo* (*J. Vascular Research,* vol. 32, p. 79 (1995)). It has been reported that 20-HETE induces constriction or dilation of microvessels in major organs such as the kidneys and the cerebral blood vessels, and causes cell proliferation, and it is suggested that 20-HETE plays important physiological roles *in vivo,* and participates in various kidney diseases, cerebrovascular diseases, and circulatory diseases (*J. Vascular Research,* vol. 32, p. 79 (1995); *Am. J. Physiol.*, vol. 277, p. R607 (1999); and the like).

Disclosure of the Invention

[0003] An object of the present invention is to provide a pharmaceutical agent for inhibiting the production of 20-HETE which participates in constriction or dilation of microvessels in major organs such as the kidneys and the cerebral blood vessels, or participates in causing cell proliferation.

[0004] As a result of various studies in order to solve the above problem, the present inventors have discovered that aromatic compounds having a specific substructure, and in particular, hydroxyformamidine compounds as pyridine derivatives, unexpectedly possess the inhibitory activity for 20-HETE synthase, to accomplish the present invention.

[0005] That is, the present invention relates to a hydroxyformamidine compound represented by the general formula (I) as follows:



wherein R^1 is a group represented by the formula: R^2-$(CH_2)_m$-(wherein R^2 is a C_{3-8} cycloalkyl group, a C_{2-6} alkoxycarbonyl group, a C_{2-10} alkenyl group, a C_{2-6} alkynyl group, a substituted or non-substituted aryl group, a furyl group, an oxolanyl group, a substituted or non-substituted dioxolanyl group, an oxanyl group, a substituted or non-substituted dioxanyl group, a benzodioxanyl group, a piperidyl group, an N-(C_{1-6} alkyl)piperidyl group, a substituted or non-substituted pyridyl group, a thienyl group, a substituted or non-substituted thiazolyl group, or a bicyclo[2.2.1]heptanyl group, and m is an integer of 1 to 8), a group represented by the formula: R^3-A- (wherein R^3 is a hydrogen atom, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, a di(C_{1-6} alkyl)amino group, a substituted or non-substituted arylamino group, a C_{1-6} alkyl (substituted or non-substituted aryl)amino group, a C_{1-6} alkylthio group, a C_{1-6} alkoxy C_{1-6} alkoxy group, a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group, a hydroxy group, an acetoxy group, an arylthio group, an aryloxy group, a phthalimidoyl group, a piperidino group, a pyridylthio group, a pyrrolidinyl group, a pyrrolyl group, a morpholino group, or a substituted or non-substituted 2,6-purindion-7-yl group, and A is a straight-chain C_{2-10} alkylene group which may be substituted with a C_{1-6} alkyl group or a trifluoromethyl group), or a C_{3-8} cycloalkyl group, and X is an oxygen atom or a sulfur atom, or a pharmaceutically acceptable salt thereof.

[0006] In the compounds of the general formula (I) described above, it is preferable that X is an oxygen atom. In addition, it is more preferable that X is an oxygen atom and R^1 is a group represented by the formula:

R^4-B- (wherein R^4 is a di(C_{1-6} alkyl)amino group, a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group, a piperidino group, a pyrrolidinyl group, or a morpholino group, and B is a straight-chain C_{2-6} alkylene group which may be substituted with one or two methyl groups).

[0007] The hydroxyformamidine compounds or pharmaceutically acceptable salts thereof described above are employed in a medicament comprising them as active ingredients.
Preferably, they are employed as an inhibitor for production of 20-hydroxyeicosatetraenoic acid (20 HETE), or are employed as a therapeutic agent for kidney diseases, cerebrovascular diseases, or circulatory diseases.

[0008] The terms used in the present invention are defined in the following. In the present invention, "C_{x-y}" means that the group following the "C_{x-y}" has a number of carbon atoms x - y.

[0009] The C_{1-6} alkyl group means a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms. A C_{1-4} alkyl group is preferable. As examples of C_{1-6} alkyl groups, mention may be made of, for example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a *n*-butyl group, a *sec-butyl* group, a tert-butyl group, a pentyl group, an isopentyl group, a hexyl group, an isohexyl group, and the like.

[0010] The C_{1-6} alkoxy group means a straight-chain or branched-chain alkoxy group having 1 to 6 carbon atoms. A C_{1-4} alkoxy group is preferable. As examples of C_{1-6} alkoxy groups, mention may be made of, for example, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a *tert*-butoxy group, a pentyloxy group, an isopentyloxy group, and the like.

[0011] The C_{1-6} alkylthio group has a combined structure of a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms and one thio group (-S-). A C_{1-4} alkylthio group is preferable. As examples of C_{1-6} alkylthio groups, mention may be made of, for example, a methylthio group, an ethylthio group, a propylthio group, and the like.

[0012] The C_{3-8} cycloalkyl group refers to a cyclic alkyl group having 3 to 8 carbon atoms, and also includes a group with a structure having bridged ring(s). As examples of C_{3-8} cycloalkoxy groups, mention may be made of, for example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, and the like.

[0013] The C_{3-8} cycloalkoxy group has a combined structure of a cyclic alkyl group having 3 to 8 carbon atoms and one oxy group (-O-). As examples of C_{3-8} cycloalkoxy groups, mention may be made of, for example, a cyclopropyloxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cycloheptyloxy group, and the like.

[0014] The di(C_{1-6} alkyl)amino group has a structure wherein each of two hydrogen atoms present on the amino group (-NH_2) is independently substituted with a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms. A di(C_{1-4} alkyl)amino group is preferable. As examples of di(C_{1-6} alkyl)amino groups, mention may be made of, for example, an N,N-dimethylamino group, an N,N-diethylamino group, and the like.

[0015] The C_{2-6} alkoxycarbonyl group has a combined structure of a straight-chain or branched-chain alkoxy group having 1 to 5 carbon atoms and one carbonyl group (-CO-). A C_{2-4} alkoxycarbonyl group is preferable. As examples of C_{2-6} alkoxycarbonyl groups, mention may be made of, for example, a methoxycarbonyl group, an ethoxycarbonyl group, and the like.

[0016] The C_{1-6} alkoxy C_{1-6} alkoxy group has a combined structure of a C_{1-6} alkoxy group and a C_{1-6} alkoxy group. A C_{1-4} alkoxy C_{1-6} alkoxy group is preferable. As examples of C_{1-6} alkoxy C_{1-6} alkoxy groups, mention may be made of, for example, a methoxyethoxy group, an ethoxyethoxy group, and the like.

[0017] The di(C_{1-6} alkyl)amino C_{1-6} alkoxy group has a combined structure of a di(C_{1-6} alkyl)amino group and a C_{1-6} alkoxy group. A di(C_{1-4} alkyl)amino C_{1-4} alkoxy group is preferable. As examples of di(C_{1-6} alkyl)amino C_{1-6} alkoxy groups, mention may be made of, for example, an N,N-dimethylaminoethoxy group, an N,N-diethylaminoethoxy group, an N,N-diethylaminoethoxy group, and the like.

[0018] The C_{2-10} alkenyl group refers to a straight-chain or branched-chain alkenyl group having at least one double bond and having 2 to 10 carbon atoms. As examples of C_{2-10} alkenyl groups, mention may be made of, for example, an ethenyl group, a 1-propenyl group, a 2-propenyl group, a 2-methyl-1-propenyl group, a 1-butenyl group, a 3-butenyl group, *cis-cis*- and *trans-cis*-2,6-dimethyl-1,5-heptadienyl groups, a 2,6-dimethyl-5-heptenyl group, a 1,3-pentadienyl group, a 1,5-dimethyl-4-hexenyl group, and the like.

[0019] The C_{2-6} alkynyl group refers to a straight-chain or branched-chain alkynyl group having at least one triple bond and having 2 to 6 carbon atoms. As examples of C_{2-6} alkynyl groups, mention may be made of, for example, an ethynyl group, a 1-propynyl group, a 2-propynyl group, a 2-butynyl group, a 3-butynyl group, and the like.

[0020] The bicyclo[2.2.1]heptanyl group corresponds to a bicyclo-type saturated and bridged cyclic hydrocarbon group. As an example thereof, mention may be made of, for example, a bicyclo[2.2.1]hepta-2-yl group, or the like.

[0021] The "aryl" refers to a mono-valent group of an aromatic hydrocarbon such as phenyl, naphthyl, or the like. Therefore, in the present invention, the aryl group is a phenyl group, a naphthyl group, or the like, and preferably is a phenyl group. The substituted aryl group means a group wherein at least one hydrogen atom present on the ring thereof is substituted with a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{2-6} alkoxycarbonyl group, an aryl group, an aryloxy group, a phenethyl group, a cyano group, or a halogen atom. As the C_{1-6} alkyl group, the C_{1-6} alkoxy group, and the C_{2-6} alkoxycarbonyl group for the substituents, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, and a C_{2-4} alkoxycarbonyl group are preferable, respectively. In particular, a methyl group, a methoxy group, and a methoxycarbonyl group are preferable, respectively. In addition, as the aryl group and the aryloxy group for the substituents, a phenyl group and a phenoxy group are preferable, respectively. The halogen atom may be a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom, is preferably a fluorine atom, a chlorine atom, or a bromine atom, and is more preferably a

fluorine atom or a chlorine atom.

[0022] As examples of the substituted aryl groups, mention may be made of a 3-methylphenyl group, a 4-methylphenyl group, a 2,3-dimethoxyphenyl group, a 3,4-dimethoxyphenyl group, a 4-methoxyphenyl group, a 3-methoxyphenyl group, a 2-methoxyphenyl group, a 3-phenoxyphenyl group, a biphenyl group, a 3-bromophenyl group, a 4-bromophenyl group, a 2,5-difluorophenyl group, a 2,4-dichlorophenyl group, a 4-fluorophenyl group, and the like.

[0023] The substituted or non-substituted arylamino group has a structure wherein one hydrogen atom of the amino group ($-NH_2$) is substituted with a substituted or non-substituted aryl group. As examples thereof, mention may be made of, for example, a phenylamino group, a 3-methylphenylamino group, and the like.

[0024] The C_{1-6} alkyl (substituted or non-substituted aryl)amino group has a structure wherein one hydrogen atom of the amino group ($-NH_2$) is substituted with a straight-chain or branched-chain alkyl group having 1 to 6 carbon atoms, and the other hydrogen atom thereof is substituted with a substituted or non-substituted aryl group. As an example thereof, mention may be made of, for example, an N-ethyl-N-(3-methylphenyl)amino group, or the like.

[0025] The arylthio group has a combined structure of an aryl group and one thio group (-S-). As examples thereof, mention may be made of, for example, a phenylthio group, a naphthylthio group, and the like.

[0026] The aryloxy group has a combined structure of an aryl group and one oxy group (-O-). As examples thereof, mention may be made of, for example, a phenoxy group, a naphthoxy group, and the like.

[0027] The furyl group includes a 2-furyl group or a 3-furyl group.

[0028] The oxolanyl group has a structure of a saturated 5-membered ring having one oxygen atom (O) as a hetero atom, and includes a 2-oxolanyl group, or a 3-oxolanyl group.

[0029] The dioxolanyl group has a structure of a saturated 5-membered ring having two oxygen atoms (O) as hetero atoms (dioxolane), and preferably refers to a mono-valent group derived by eliminating a hydrogen atom from a 1,3-dioxolane ring. The substituted dioxolanyl group means a group wherein at least one hydrogen atom present on the group described above is substituted with a C_{1-6} alkyl group and preferably a C_{1-4} alkyl group. As an example thereof, a 2,2-dimethyl-1,3-dioxolan-4-yl group or the like may be given.

[0030] The oxanyl group has a structure of a saturated 6-membered ring having one oxygen atom (O) as a hetero atom. As examples thereof, mention may be made of, for example, a 2-oxanyl group, a 3-oxanyl group, a 4-oxanyl group, and the like.

[0031] The dioxanyl group has a structure of a saturated 6-membered ring having two oxygen atoms (O) as hetero atoms (dioxane). Preferably, it refers to a mono-valent group derived by eliminating a hydrogen atom from a 1,3-dioxane ring. The substituted dioxanyl group means a group wherein at least one hydrogen atom present on the group described above is substituted with a C_{1-4} alkyl group. As an example thereof, a 5,5-dimethyl-1,3-dioxan-2-yl group or the like may be given.

[0032] The benzodioxanyl group refers to a mono-valent group derived by eliminating a hydrogen atom from a benzodioxane ring and preferably a 1,4-benzodioxane ring. As an example thereof, a 1,4-benzodioxan-2-yl group or the like may be given.

[0033] The phthalimidoyl group refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom of phthalimide.

[0034] The piperidino group refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom of piperidine.

[0035] The piperidyl group refers to a mono-valent group derived by eliminating a hydrogen atom present on the carbon atom of piperidine. The N-(C_{1-6} alkyl)piperidyl group means a group wherein the nitrogen atom of a piperidyl group is substituted with a C_{1-6} alkyl group. As examples thereof, mention may be made of, for example, a 3-(N-methylpiperidyl) group, a 4-(N-methylpiperidyl) group, and the like.

[0036] The pyridyl group includes a 2-pyridyl group, a 3-pyridyl group, or a 4-pyridyl group. In addition, the substituted pyridyl group means a group wherein at least one hydrogen atom present on the ring is substituted with a C_{1-6} alkyl group, preferably a C_{1-4} alkyl group, and more preferably a methyl group. As an example thereof, a 6-methyl-2-pyridyl group or the like may be given.

[0037] The pyridylthio group has a combined structure of a pyridyl group and one thio group (-S-). As examples thereof, mention may be made of, for example, a pyridin-2-ylthio group, a pyridin-3-ylthio group, a pyridin-4-ylthio group, and the like. A pyridin-2-ylthio group is preferable.

[0038] The pyrrolidinyl group refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom or the carbon atom of a pyrrolidine ring. As examples thereof, mention may be made of, for example, a 1-pyrrolidinyl group, a 2-pyrrolidinyl group, a 3-pyrrolidinyl group, and the like. A 1-pyrrolidinyl group is preferable.

[0039] The pyrrolyl group includes a 1-pyrrolyl group, a 2-pyrrolyl group, or a 3-pyrrolyl group. A 1-pyrrolyl group (N-pyrrolyl group) is preferable.

[0040] The thienyl group includes a 2-thienyl group, or a 3-thienyl group.

[0041] The thiazolyl group includes a 2-thiazolyl group, a 4-thiazolyl group, or a 5-thiazolyl group. In addition, the substituted thiazolyl group means a group wherein at least one hydrogen atom present on the ring is substituted with

a C_{1-6} alkyl group and preferably a C_{1-4} alkyl group. As an example thereof, a 4-methyl-5-thiazolyl group or the like may be given.

[0042] The morpholino group refers to a mono-valent group derived by eliminating a hydrogen atom present on the nitrogen atom of morpholine.

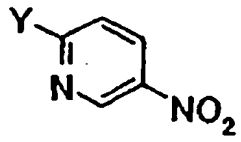
[0043] The 2,6-purindion-7-yl group refers to a mono-valent group derived from 2,6-purindione wherein one oxygen atom (=O) is bonded to the carbon atom at the 2-position of the purine ring and one oxygen atom (=O) is bonded to the carbon atom at the 6-position of the purine ring, and refers to a group derived by eliminating a hydrogen atom present on the nitrogen atom at the 7-position. The substituted 2,6-purindion-7-yl means a group wherein at least one of the hydrogen atoms bonded to the nitrogen atom of the group is substituted with a C_{1-6} alkyl group, preferably a C_{1-4} alkyl group, and more preferably a methyl group. As an example thereof, a 1,3-dimethyl-2,6-purindion-7-yl group or the like may be given.

[0044] The "straight-chain C_{2-10} alkylene group which may be substituted with a C_{1-6} alkyl group or a trifluoromethyl group" defined in "A" means a straight-chain alkylene group having 2 to 10 carbon atoms, which may be substituted with one or more groups, and preferably one or two groups selected from straight-chain or branched-chain alkyl groups having 1 to 6 carbon atoms and trifluoromethyl groups. Among these, a straight-chain C_{2-6} alkylene group which may be substituted with one or two methyl groups defined in "B" is preferable. As examples thereof, mention may be made of an ethylene group, a 1-methylethylene group, a propylene group, a 2,2-dimethylpropylene group, a butylene group, a 1-methylbutylene group, a hexylene group, a 1-trifluoromethylpropylene group, a heptylene group, a 4-methylpentylene group, a 3-methylbutylene group, a 1-methylpropylene group, a 3-methylpentylene group, a 1,1-dimethylethylene group, and the like. A 2,2-dimethylpropylene group, a hexylene group, and the like are preferable.

[0045] In addition, the pharmaceutically acceptable salt refers to a salt with an alkali metal, an alkali earth metal, ammonium, an alkylammonium, or the like, as well as, a salt with a mineral acid or an organic acid. As examples thereof, mention may be made of, for example, a sodium salt, a potassium salt, a calcium salt, an ammonium salt, an aluminum salt, a triethylammonium salt, an acetate, a propionate, a butyrate, a formate, a trifluoroacetate, a maleate, a tartarate, a citrate, a stearate, a succinate, an ethylsuccinate, a lactobionate, a gluconate, a glucoheptonate, a benzoate, a methanesulfonate, an ethanesulfonate, a 2-hydroxyethanesulfonate, a benzenesulfonate, a para-toluenesulfonate, a laurylsulfate, a malate, an aspartate, a glutamate, an adipate, a salt with a cysteine, a salt with an N-acetylcysteine, a hydrochloride, a hydrobromide, a phosphates, a sulfate, a hydroiodide, a nicotinate, an oxalate, a picrate, a thiocyanate, an undecanate, a salt with a polymeric acrylic acid, a salt with a carboxyvinyl polymer, and the like.

[0046] The compounds of the present invention can be synthesized according to, for example, the methods described below.

[0047] First, a compound represented by the formula (a) described below:

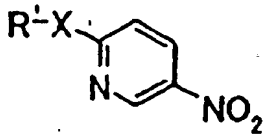


(a)

[wherein Y represents a halogen atom of any one of F, Cl, Br and I] and a compound represented by the formula (b) described below:

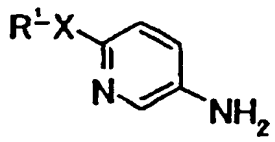
$$R^1XH \qquad (b)$$

[wherein R^1 and X have the same meanings as described above] are reacted in the presence of an appropriate base to produce a compound represented by the formula (c) described below:



(c)

[0048] Subsequently, according to a common method for reducing an aromatic nitro group to an aromatic amino group, the compound represented by the above formula (c) is derived to a compound represented by the formula (d) described below:



(d)

[0049] Subsequently, the compound represented by the above formula (d) is reacted with dimethylformamide dimethylacetal in the presence or absence of an appropriate solvent for 2 to 72 hours at a temperature in the range of room temperature to 150°C, and preferably in the range of 70 to 100°C to obtain an intermediate. Subsequently, by treating the intermediate, after isolation or in the state as produced, with hydroxylamine or a salt thereof such as a hydrochloride in a solvent such as methanol, the compound of the present invention can be synthesized.

[0050] Alternatively, the compound represented by the above formula (d) is reacted with an orthoformate such as trimethyl orthoformate, triethyl orthoformate, or the like in the presence of a catalytic amount of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid, or a salt of a mineral acid and an amine such as pyridine hydrochloride, for 2 to 72 hours at a temperature in the range of room temperature to 150°C, and preferably in the range of 70 to 100°C to obtain an intermediate. Subsequently, by treating the intermediate, after isolation or in the state as produced, with hydroxylamine in a solvent such as methanol, the compound of the present invention can be synthesized. As described above, the compounds of the present invention can be synthesized from the compounds represented by the above formula (d) using a common method for converting an amino group present on an aromatic ring into an N-hydroxyformamidine group.

[0051] The compounds and the pharmaceutically acceptable salts thereof according to the present invention can be administered orally,or parenterally, in the form of tablets, capsules, granules, powders, troches, ointments, creams, emulsions, suspensions, suppositories, injectable solutions, or the like, each of which may be produced according to the conventional formulation methods (for example, methods defined in the 12th revision of Japanese Pharmacopeia). These preparation forms may be selected depending on the conditions and ages of the patients, as well as the purpose of the treatment. Upon manufacturing preparations in various formulations, conventional fillers (for example, crystalline cellulose, starch, lactose, mannitol, or the like), binders (for example, hydroxypropylcellulose, polyvinylpyrrolidone, or the like), lubricants (for example, magnesium stearate, talc, or the like), disintegrants (for example, carboxymethylcellulose calcium, or the like), and the like, may be employed.

[0052] The dose of the compounds and the pharmaceutically acceptable salts thereof according to the present invention is preferably in the range of 1 to 2000 mg per day in the case of an adult human subject to be treated. They may be administered in a single dose or divided into several doses per day. The doses may appropriately vary depending on the age, weight, and conditions of each individual patient, and the like.

Best Modes for Carrying out the Invention

[0053] In the following, the present invention is illustrated in detail with reference to the following examples.

Example 1:

Synthesis of N-[2-(2-butyn-1-oxy)pyridin-5-yl]-N'-hydroxyformamidine (Compound 65)

[0054] Sodium hydride (60% in oil) (0.91 g, 22.7 mmol) was washed with dry hexane, and dimethylformamide (15 ml) and 2-butyn-1-ol (1.59 g, 22.7 mmol) were added thereto. The mixture was stirred for 1 hour at room temperature. The reaction mixture was cooled to 0°C, and a solution of 2-chloro-5-nitropyridine (3g, 18.9 mmol) in dimethylformamide (20 ml) was added dropwise thereto. The mixture was stirred for 1 hour at room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over $MgSO_4$, and was subsequently concentrated under reduced pressure. Subsequently, iron powders (10.55 g, 189 mmol), isopropanol (10 ml), and a 1N aqueous solution of ammonium chloride (11.3 ml, 11.3 mmol) were added thereto. The mixture was stirred for 1 hour at 85°C. Ethyl acetate (100ml) was added to the reaction mixture, and insoluble materials were removed therefrom by filtration with a celite. The filtrate was concentrated under reduced pressure, and subsequently a saturated aqueous solution of sodium hydrogencarbonate (20 ml) was added thereto, followed by extraction with ethyl acetate.

The organic layer was dried over $MgSO_4$, and was subsequently concentrated under reduced pressure. Subsequently, ethyl orthoformate (6.27 ml) was added thereto, and the mixture was stirred for 16 hours at 100°C. The reaction mixture was concentrated under reduced pressure. Subsequently, a 1N methanol solution of hydroxylamine (22.78 ml) was added thereto, and the mixture was stirred for one hour at room temperature. The reaction mixture was concentrated under reduced pressure to yield a crude product. The crude product was purified by NH type silica gel column chromatography (eluent, hexane:ethyl acetate = 1:1), and was subsequently recrystallized from ethyl acetate/hexane to yield the target compound (Compound 65 in Table 1 described below) as of a colorless powder (0.654 g).

Melting point: 155.5 to 157.0°C

Example 2:

Synthesis of N-[2-(3-dimethylamino-2,2-dimethylpropyl-l-oxy)pyridin-5-yl]-N'-hydroxyformamidine (Compound 123)

[0055] A mixture of 3-dimethylamino-2,2-dimethyl-1-propanol (82.8 g, 630 mml) and 2-chloro-5-nitropyridine (20 g, 126 mmol) was stirred for 6 hours at 100°C. Water was added to the reaction mixture, and the resulting precipitated crystals were obtained by filtration. The precipitate was dried, and methanol (330 ml) and palladium carbon (1.4 g) were added thereto. The mixture was stirred for 2 hours at room temperature. Subsequently, insoluble materials were removed therefrom by filtration with celite. The filtrate was concentrated under reduced pressure. Subsequently, methanol (250 ml) and dimethylformamide dimethylacetal (15.9 g, 133 mmol) were added thereto, and the mixture was stirred under reflux for 3 hours. The reaction mixture was cooled to room temperature. Subsequently, hydroxylamine hydrochloride (9.24 g, 133 mmol) was added thereto, and the mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and subsequently a saturated aqueous solution of sodium hydrogencarbonate (10 ml) was added thereto, followed by extraction with ethyl acetate. The organic layer was dried over $MgSO_4$, and was subsequently concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to yield the target compound (Compound 123 in Table 1 described below) as of a colorless powder (19.04 g).

Melting point: 74.0 to 76.5°C

Example 3:

Synthesis of N-[2-(pyridin-2-ylmethoxy)pyridin-5-yl]-N'-hydroxyformamidine (Compound 6)

[0056] A mixture of 5-amino-2-(pyridin-2-ylmethoxy)pyridine (1.10 g) and ethyl orthoformate (1.782 g) was stirred for 8 hours at 100°C. Subsequently, excess ethyl orthoformate was removed. The residue in methanol (20ml) was added a 1 M methanol solution of hydroxylamine (8.2 ml). The mixture was stirred for 1 hour at room temperature. After removal of the solvent, chloroform was added to the obtained residue. The mixture was washed successively with water and saturated brine, and was subsequently dried over anhydrous sodium sulfate, followed by removal of the solvent. The obtained residue was recrystallized from chloroform to yield the target compound (Compound 6 in Table 1 described below) as of a colorless powder (0.374 g).

Melting point: 153.5 to 155.5°C

Example 4:

Synthesis of N-[2-(benzylthio)pyridin-5-yl]-N'-hydroxyformamidine (Compound 104)

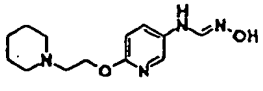
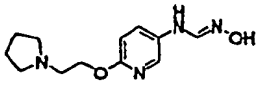
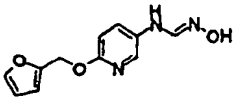
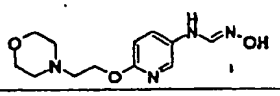
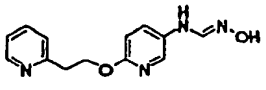
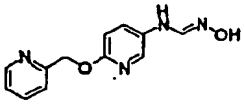
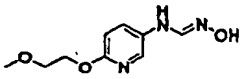
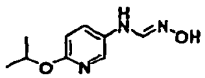
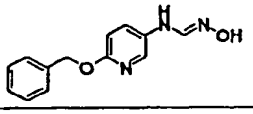
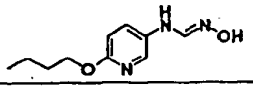
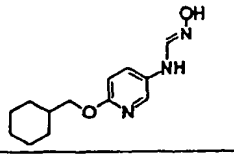
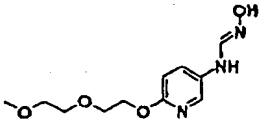
[0057] A mixture of 5-amino-2-(benzylthio)pyridine (1.11 g) and ethyl orthoformate (1.78 g) was stirred for 8 hours at 100°C. Subsequently, excess ethyl orthoformate was removed. The residue in methanol (20ml) was added a 1 M methanol solution of hydroxylamine (8.2 ml). The mixture was stirred for 1 hour at room temperature. After removal of the solvent, chloroform was added to the obtained residue. The mixture was washed successively with water and saturated brine, and was subsequently dried over anhydrous sodium sulfate, followed by removal of the solvent. The obtained residue was recrystallized from chloroform to yield the target compound (Compound 104 in Table 1 described below) as of a colorless powder (0.45 g).

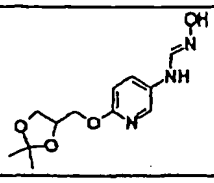
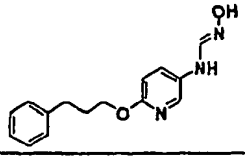
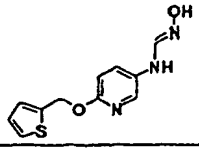
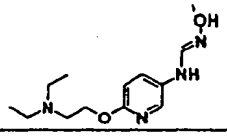
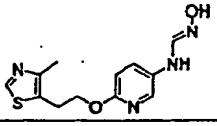
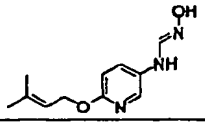
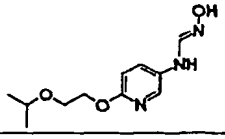
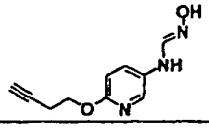
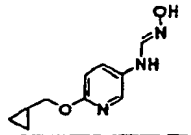
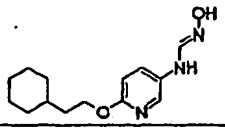
Melting point: 133.0 to 135.0°C

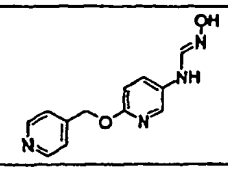
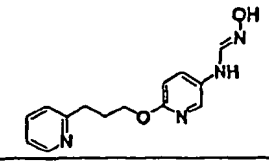
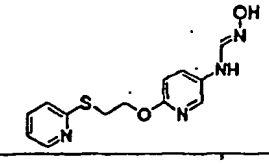
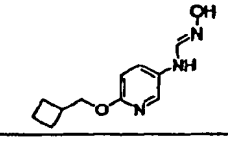
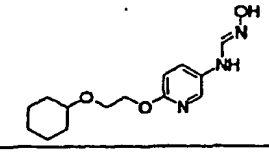
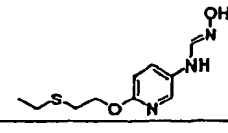
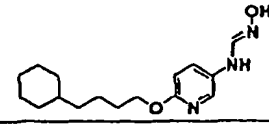
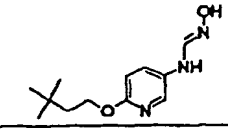
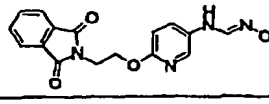
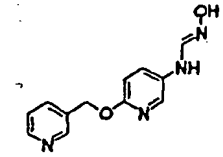
Examples 5 to 134:

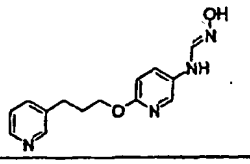
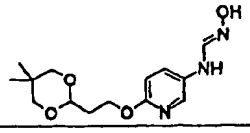
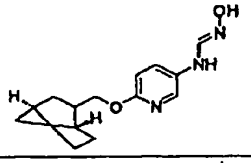
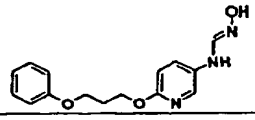
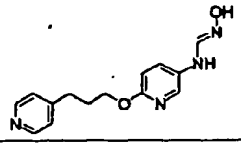
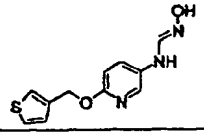
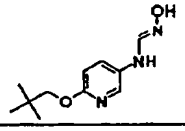
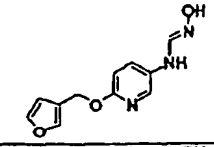
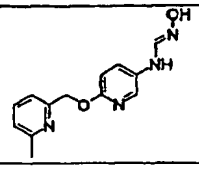
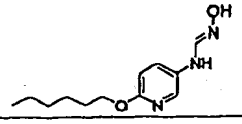
[0058] In the following, the compounds shown in Table 1 described below were synthesized by carrying out similar reaction procedures to those of Examples 1 to 4 employing the corresponding starting materials.

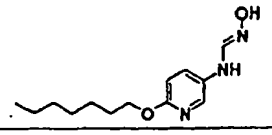
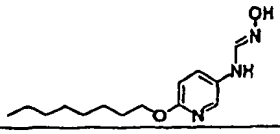
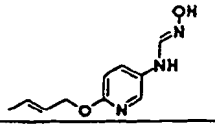
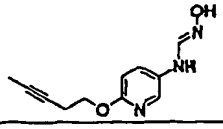
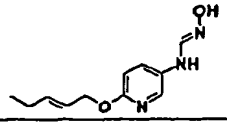
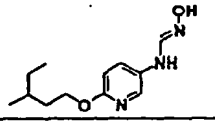
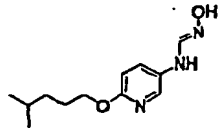
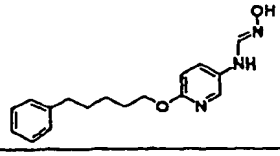
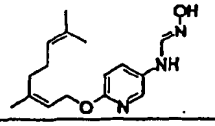
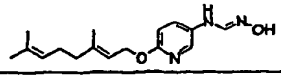
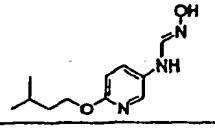
Table 1

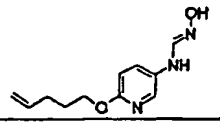
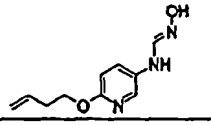
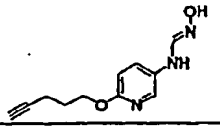
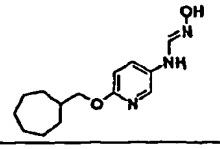
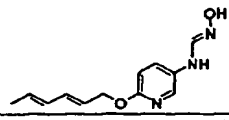
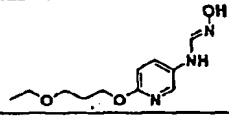
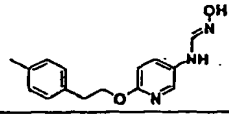
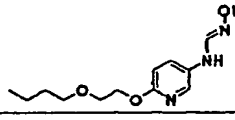
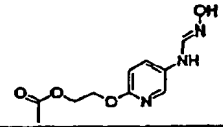
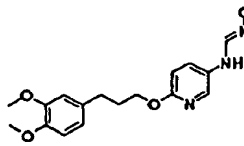
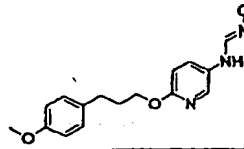
Comp. No.	Chemical Structure	m.p.	M+H (ESI)	M+H (APCI)	M-H (ESI)	M-H (APCI)	Rf Value	TLC*	Eluent	Inhibition (1M)	IC50 (nM)
Comp. 1		133.5–135.5	264		262		0.11	SiO2	AcOEt	61.0	738.4
Comp. 2		130.5–132.5	250		248		0.07	SiO2	AcOEt	97.0	3095
Comp. 3			233				0.11	SiO2	AcOEt	102.0	49.6
Comp. 4		158.5–160.0	266		264		0.09	SiO2	AcOEt	99.0	339.2
Comp. 5		128.5–130.0									14.9
Comp. 6		153.5–155.5	244				0.1	SiO2	AcOEt	65.0	514.4
Comp. 7		104.5–106.0								41.9	781.4
Comp. 8		116.5–117.0								71.0	603.3
Comp. 9		163.5–164.0								82.9	9.1
Comp. 10		127.0–128.0								106.3	167.4
Comp. 11		156.5–157.0	249		247		0.17	SiO2	AcOEt	89.0	2.7
Comp. 12		90.0–91.5	255		253		0.14	SiO2	AcOEt	99.0	87.2

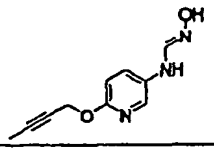
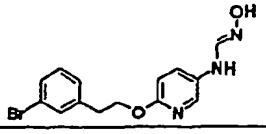
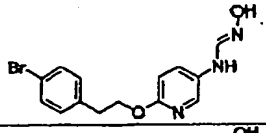
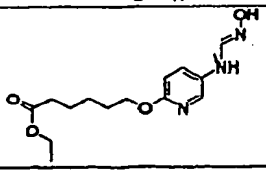
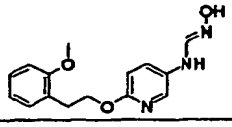
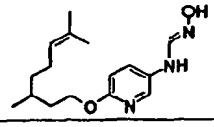
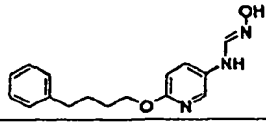
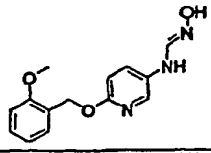
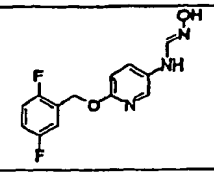
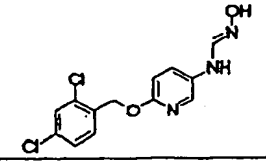
Comp. 13		97.0-97.5	267		265		0.18	SiO2	AcOEt	101.0	24.0
Comp. 14		125.0-126.0	271		269		0.18	SiO2	AcOEt	104.0	1.5
Comp. 15		159.0-160.0	249				0.15	SiO2	AcOEt	100.0	9.3
Comp. 16			252		250		0.14	SiO2	AcOEt	60.0	
Comp. 17		159.0-160.0	278		276		0.1	SiO2	AcOEt	100.0	2.1
Comp. 18			221				0.17	SiO2	AcOEt	86.0	
Comp. 19			239		237		0.17	SiO2	AcOEt	104.0	
Comp. 20			205		203		0.17	SiO2	AcOEt	31.0	
Comp. 21			207		205		0.15	SiO2	AcOEt	73.0	
Comp. 22		125.2-126.0	263		261		0.17	SiO2	AcOEt	108.0	2.1

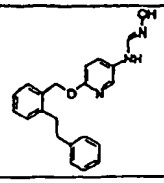
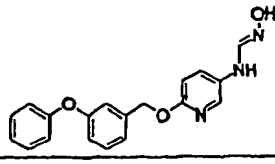
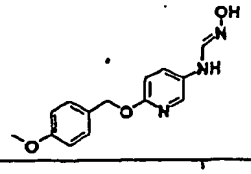
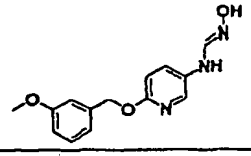
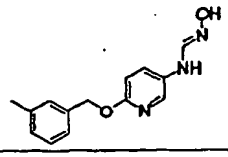
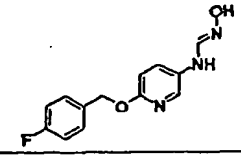
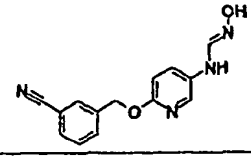
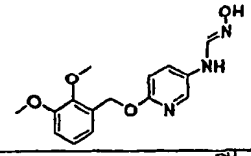
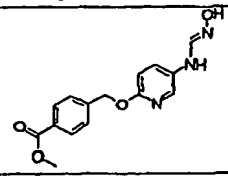
Comp. 23		192.0–192.5	244		242		0.09	SiO2	AcOEt	104.0	3.9
Comp. 24			272		270		0.17	SiO2	AcOEt		
Comp. 25		134.0–135.0	290		288		0.13	SiO2	AcOEt	71.0	9.6
Comp. 26		136.0–138.0	221		219		0.17	SiO2	AcOEt	99.0	27.2
Comp. 27			279		277		0.16	SiO2	AcOEt	71.0	
Comp. 28		104.0–105.0	241		239		0.15	SiO2	AcOEt	105.0	9.9
Comp. 29			291		289		0.19	SiO2	AcOEt	101.0	
Comp. 30			237		235		0.19	SiO2	AcOEt	102.0	
Comp. 31			326		324		0.1	SiO2	AcOEt	40.0	
Comp. 32			244		242		0.08	SiO2	AcOEt		

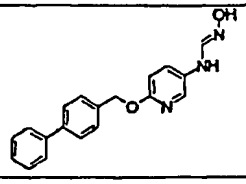
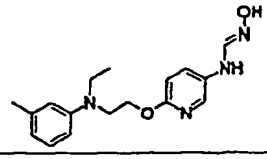
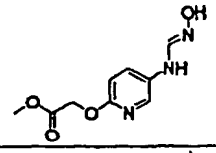
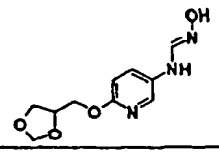
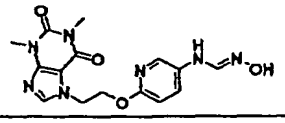
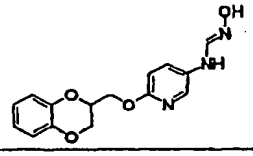
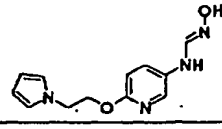
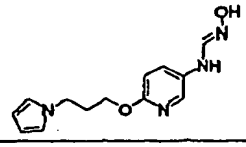
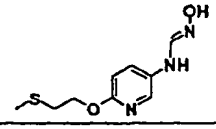
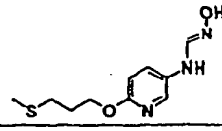
Comp. 33		122.0–123.0	272		270		0.1	SiO2	AcOEt	93.0	2.1
Comp. 34		107.0–108.0	295		293		0.17	SiO2	AcOEt	89.0	7.6
Comp. 35			261		259		0.18	SiO2	AcOEt	98.0	
Comp. 36		145.0–146.0	287		285		0.18	SiO2	AcOEt	104.0	2.7
Comp. 37		181.5–183.5	272		270		0.08	SiO2	AcOEt	98.0	3.4
Comp. 38		169.5–170.0	249		247		0.16	SiO2	AcOEt	95.0	8.5
Comp. 39			223		221		0.19	SiO2	AcOEt	62.0	
Comp. 40			233		231		0.15	SiO2	AcOEt	86.0	
Comp. 41			258		256		0.14	SiO2	AcOEt	83.0	
Comp. 42			238		236		0.24	SiO2	AcOEt	105.8	

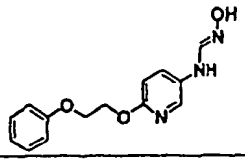
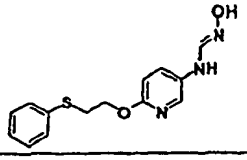
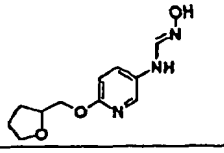
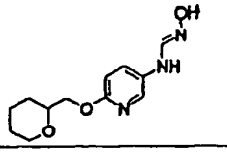
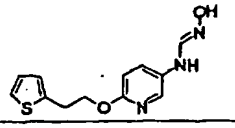
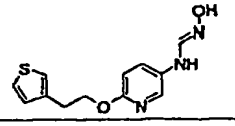
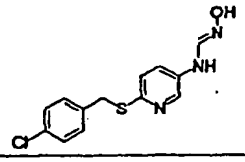
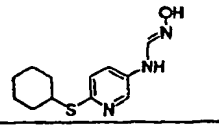
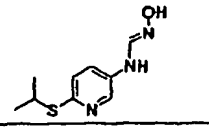
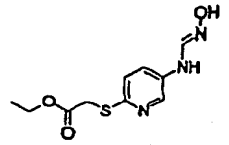
Comp. 43			252		250		0.24	SiO2	AcOEt	89.5	
Comp. 44			266		264		0.25	SiO2	AcOEt	100.7	
Comp. 45		143.0–144.5	208		206		0.21	SiO2	AcOEt	80.3	10.7
Comp. 46		151.0–152.0	220				0.20	SiO2	AcOEt	89.9	9.8
Comp. 47		82.0–84.0	222		220		0.23	SiO2	AcOEt	99.2	45.4
Comp. 48			238		236		0.23	SiO2	AcOEt	102.8	
Comp. 49			238		236		0.23	SiO2	AcOEt	107.1	
Comp. 50			300		298		0.23	SiO2	AcOEt	108.2	
Comp. 51					288		0.25	SiO2	AcOEt	111.0	
Comp. 52					288		0.24	SiO2	AcOEt	108.7	
Comp. 53		123.0–125.0	224		222		0.23	SiO2	AcOEt	108.5	6.8

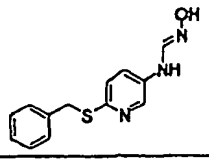
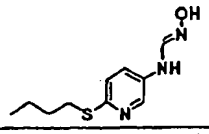
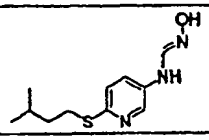
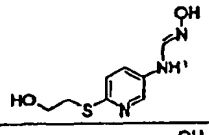
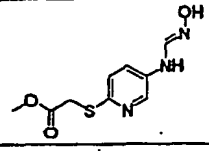
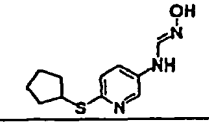
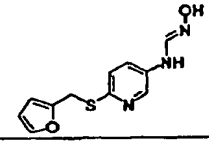
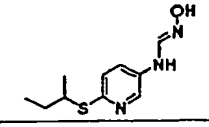
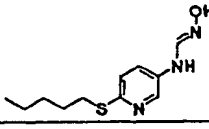
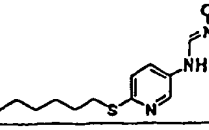
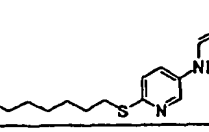
Comp. 54		120.0–122.0	222		220		0.22	SiO2	AcOEt	111.7	5.9
Comp. 55		119.0–120.0	208		208		0.22	SiO2	AcOEt	87.3	
Comp. 56		124.5–125.5	220		218		0.21	SiO2	AcOEt	102.1	14.7
Comp. 57			264		262		0.22	SiO2	AcOEt	114.2	
Comp. 58			234		232		0.2	SiO2	AcOEt	106.6	
Comp. 59		99.0–100.0	240		238		0.20	SiO2	AcOEt	109.6	4.4
Comp. 60			272		270		0.21	SiO2	AcOEt	109.9	
Comp. 61		113.0–114.5	254		252		0.21	SiO2	AcOEt	99.8	13.1
Comp. 62			240		238		0.18	SiO2	AcOEt	112.8	
Comp. 63			332		330		0.17	SiO2	AcOEt	102.3	
Comp. 64			302		300		0.21	SiO2	AcOEt	100.7	

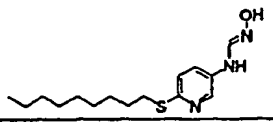
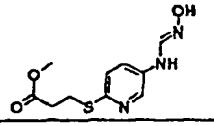
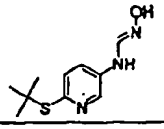
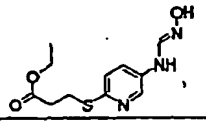
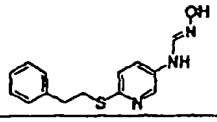
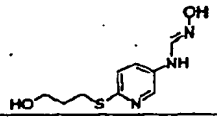
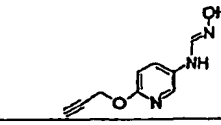
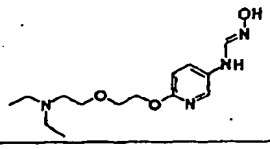
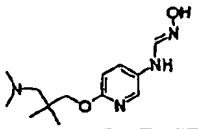
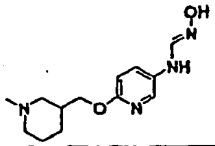
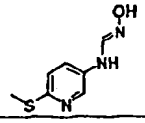
Comp. 65		155.5-157.0	206				0.21	SiO2	AcOEt	86.9	68.2
Comp. 66			337		335		0.20	SiO2	AcOEt	105.3	
Comp. 67			337		335		0.20	SiO2	AcOEt	108.6	
Comp. 68			298		294		0.20	SiO2	AcOEt	102.6	
Comp. 69		159.5-161.0	288		286		0.18	SiO2	AcOEt	102.8	6.5
Comp. 70			292		290		0.24	SiO2	AcOEt	108.1	
Comp. 71			286		284		0.20	SiO2	AcOEt	99.0	
Comp. 72		146.5-147.5	274		272		0.18	SiO2	AcOEt	92.9	59.0
Comp. 73		158.5-159.5	280		278		0.23	SiO2	AcOEt	105.0	6.4
Comp. 74			313		311		0.20	SiO2	AcOEt	69.3	

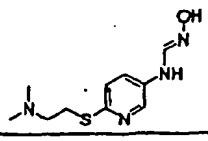
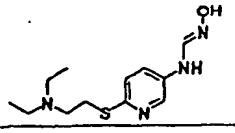
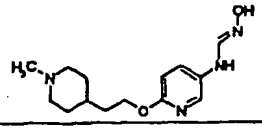
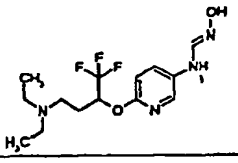
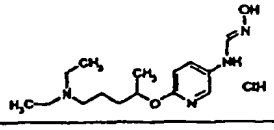
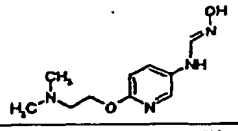
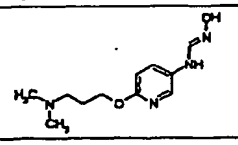
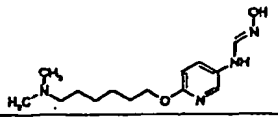
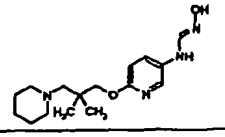
Comp. 75			348		346		0.21	SiO2	AcOEt	88.5	
Comp. 76			336		334		0.20	SiO2	AcOEt	100.2	
Comp. 77		164.5-165.5	274		272		0.20	SiO2	AcOEt	100.3	3.3
Comp. 78		126.0-127.0	274		272		0.21	SiO2	AcOEt	100.2	4.2
Comp. 79			258		256		0.21	SiO2	AcOEt	100.6	
Comp. 80		166.5-167.5	262		260		0.21	SiO2	AcOEt	102.9	3.9
Comp. 81		166.5-167.0	269				0.19	SiO2	AcOEt	104.4	1.7
Comp. 82		128.5-129.0	304				0.18	SiO2	AcOEt	104.5	60.1
Comp. 83			302				0.17	SiO2	AcOEt	98.8	

Comp. 84			320		318		0.19	SiO2	AcOEt	105.3	
Comp. 85			315		313		0.22	SiO2	AcOEt	100.8	
Comp. 86			228		224		0.20	SiO2	AcOEt	82.6	
Comp. 87		186.5-187.0	240		238		0.19	SiO2	AcOEt	87.0	264.3
Comp. 88			350		358		0.16	SiO2	AcOEt	71.8	
Comp. 89			302		300		0.20	SiO2	AcOEt		
Comp. 90		166.5-167.0	247		245		0.17	SiO2	AcOEt	105.7	4.3
Comp. 91		140.0-141.0	261		259		0.19	SiO2	AcOEt	103.0	8.4
Comp. 92		111.5-112.0	228		226		0.21	SiO2	AcOEt	87.6	71.9
Comp. 93		109.0-111.0	242		240		0.21	SiO2	AcOEt	97.4	6.6

Comp. 94		153.0–154.0	274		272		0.21	SiO2	AcOEt	100.3	3.2
Comp. 95			290		288		0.21	SiO2	AcOEt	96.5	
Comp. 96		114.0–115.0	238		236		0.18	SiO2	AcOEt	92.3	139.7
Comp. 97		149.5–152.5	252		250		0.19	SiO2	AcOEt	85.5	58.1
Comp. 98		137.5–138.5	264		262		0.20	SiO2	AcOEt	100.7	4.3
Comp. 99		138.0–140.0	264		262		0.21	SiO2	AcOEt	95.4	1.9
Comp. 100				294	292	292	0.30	SiO2 (NH)	AcOEt	79.5	
Comp. 101			252	252	250	250	0.30	SiO2 (NH)	AcOEt	91.8	
Comp. 102		141.0–142.0	212	212	210	210	0.32	SiO2 (NH)	AcOEt	74.5	18.2
Comp. 103				256	254	254	0.28	SiO2 (NH)	AcOEt	79.9	

Comp. 104		133.0–135.0		260	258	258	0.28	SiO2 (NH)	AcOEt	103.6	
Comp. 105			226	226	224	224	0.32	SiO2 (NH)	AcOEt	100.5	
Comp. 106			240	240	238	238	0.35	SiO2 (NH)	AcOEt	77.5	
Comp. 107		115.0–115.5	214	214	212	212	0.10	SiO2 (NH)	AcOEt	83.1	294.3
Comp. 108				242	240	240	0.25	SiO2 (NH)	AcOEt	89.7	
Comp. 109		153.5–154.5	238	238	236	236	0.30	SiO2 (NH)	AcOEt	82.1	11.5
Comp. 110		140.5–141.5	250	250	248	248	0.30	SiO2 (NH)	AcOEt	85.7	12.1
Comp. 111		125.5–127.5	228	228	224	224	0.35	SiO2 (NH)	AcOEt	76.8	33.8
Comp. 112			240	240	238	238	0.35	SiO2 (NH)	AcOEt	101.5	
Comp. 113			254	254	252	252	0.38	SiO2 (NH)	AcOEt	81.3	
Comp. 114				268	266	266	0.38	SiO2 (NH)	AcOEt	85.1	

Comp. 115				296	294	294	0.38	SiO2 (NH)	AcOEt	89.0	
Comp. 116			256	256		254	0.30	SiO2 (NH)	AcOEt	93.1	
Comp. 117		174.5–175.0		226	224	224	0.30	SiO2 (NH)	AcOEt	69.3	435.4
Comp. 118				270	268	268	0.32	SiO2 (NH)	AcOEt	100.7	
Comp. 119			274	274	272	272	0.32	SiO2 (NH)	AcOEt	116.1	
Comp. 120		105.0–105.5	228	228	226	226	0.13	SiO2 (NH)	AcOEt	102.0	116.7
Comp. 121		143.5–144.5	192				0.20	SiO2 (NH)	AcOEt	99.8	400.4
Comp. 122						295				99.6	623.7
Comp. 123		74.0–76.5								97.5	0.6
Comp. 124		122.0–124.0								92.6	141.6
Comp. 125				184		182	0.28	SiO2 (NH)	AcOEt		

Comp. 126		153.5–154.5									
Comp. 127		124.5–125.5									329.6
Comp. 128		131.0–133.0	279		277		0.14	SiO2 (NH)	AcOEt		311.8
Comp. 129		109.0–111.0	335		333		0.34	SiO2 (NH)	AcOEt		
Comp. 130		122(dec.)	295		293		0.32	SiO2 (NH)	AcOEt		
Comp. 131		105.0–106.0	225		223		0.11	SiO2 (NH)	AcOEt		
Comp. 132		108.0–112.0	239		237		0.11	SiO2 (NH)	AcOEt		566.2
Comp. 133		110.0–111.5	281		279		0.06	SiO2 (NH)	HexAcOEt=1:1		53.6
Comp. 134		91.0–93.0	307		305		0.29	SiO2 (NH)	AcOEt		

* SiO2: Merck pre-coated plates Silica gel 60 F254, SiO2(NH): TLC plate NH Fuji Silysia Chemical LTD.

Experimental Example [Inhibitory effect of 20-HETE synthase derived from rat kidney microsome]

[0059] Regarding the compounds listed in the Table described above, their inhibitory activities on production of 20-HETE were examined.

[0060] This examination was carried out based on the method described in *J. Pharmacol. Exp.* Ther., Vol. 268, p. 474 (1994).

[0061] The subject compound in an amount of 1 μM was added to a 50 mM of 3-morpholinopropanesulfonic acid

buffer (MOPS) (pH 7.4), containing 5 mM of magnesium chloride, and 1 mM of ethylenediaminetetraacetic acid (EDTA) disodium salt.

[0062] Subsequently, the rat kidney microsome fraction prepared from the kidney of a spontaneously hypertensive rat (male, 6 weeks of age) as an enzyme, [5,6,8,9,11,12,14,15] tritium-arachidonic acid (supplied by Amasham) as a substrate, and NADPH (supplied by Sigma) as a coenzyme were added, and were reacted for 1.5 hours at 37°C.

[0063] After the reaction was quenched by adding formic acid (supplied by Wako Pure Chemical Industries Ltd.) to the reaction solution, acetonitrile (final concentration of 50%) was added thereto, and the mixture was allowed to stand for 1.5 hours at room temperature. The amount of 20-HETE production was measured by using a high performance liquid chromatography having a detector for radioactive substances (supplied by Gilson), equipped with an ODS column (Biocyl C18, supplied by Bio-rad).

[0064] Setting an amount of 20-HETE production to 100% when no subject compound was added, the inhibition rate (%) was calculated from the amount of 20-HETE production when a subject compound was added. The results thereof are also shown in the Table described above.

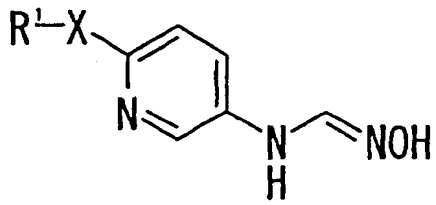
[0065] In addition, setting an amount of 20-HETE production to 100% when no subject compound was added, the concentration of the subject compound at which the production of the 20-HETE was inhibited to 50% when the subject compound is added (IC_{50} value) was also calculated. The results thereof are also shown in the Table described above.

Industrial Applicability

[0066] The compounds and the pharmaceutically acceptable salts thereof according to the present invention exhibit inhibitory activity on production of 20-HETE, and therefore, they are useful as therapeutic agents for diseases in human subjects and animals, which 20-HETE participates in, such as various kidney diseases, cerebrovascular diseases, or various circulatory diseases.

Claims

1. A hydroxyformamidine compound represented by the formula:



wherein R^1 is a group represented by the formula: R^2-$(CH_2)_m$-(wherein R^2 is a C_{3-8} cycloalkyl group, a C_{2-6} alkoxycarbonyl group, a C_{2-10} alkenyl group, a C_{2-6} alkynyl group, a substituted or non-substituted aryl group, a furyl group, an oxolanyl group, a substituted or non-substituted dioxolanyl group, an oxanyl group, a substituted or non-substituted dioxanyl group, a benzodioxanyl group, a piperidyl group, an N-(C_{1-6} alkyl)piperidyl group, a substituted or non-substituted pyridyl group, a thienyl group, a substituted or non-substituted thiazolyl group, or a bicyclo[2.2.1] heptanyl group, and m is an integer of 1 to 8), a group represented by the formula: R^3-A- (wherein R^3 is a hydrogen atom, a C_{1-6} alkoxy group, a C_{3-8} cycloalkoxy group, a di (C_{1-6} alkyl)amino group, a substituted or non-substituted arylamino group, a C_{1-6} alkyl (substituted or non-substituted aryl)amino group, a C_{1-6} alkylthio group, a C_{1-6} alkoxy C_{1-6} alkoxy group, a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group, a hydroxy group, an acetoxy group, an arylthio group, an aryloxy group, a phthalimidoyl group, a piperidino group, a pyridylthio group, a pyrrolidinyl group, a pyrrolyl group, a morpholino group, or a substituted or non-substituted 2,6-purindion-7-yl group, and A is a straight-chain C_{2-10} alkylene group which may be substituted with a C_{1-6} alkyl group or a trifluoromethyl group), or a C_{3-8} cycloalkyl group, and X is an oxygen atom. or a sulfur atom,
or a pharmaceutically acceptable salt thereof.

2. The hydroxyformamidine compound or the pharmaceutically acceptable salt thereof, according to Claim 1, **characterized in that** X is an oxygen atom.

3. The hydroxyformamidine compound or the pharmaceutically acceptable salt thereof, according to Claim 1, **char-**

acterized in that X is an oxygen atom, and R^1 is a group represented by the formula: R^4-B- (wherein R^4 is a di (C_{1-6} alkyl) amino group, a di(C_{1-6} alkyl)amino C_{1-6} alkoxy group, a piperidino group, a pyrrolidinyl group, or a morpholino group, and B is a straight-chain C_{2-6} alkylene group which may be substituted with one or two methyl groups).

4. A medicament comprising the hydroxyformamidine compound or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an active ingredient.

5. An inhibitor for production of 20-hydroxyeicosatetraenoic acid, comprising the hydroxyformamidine compound or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an active ingredient.

6. A therapeutic agent for kidney diseases, cerebrovascular diseases, or circulatory diseases, comprising the hydroxyformamidine compound or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an active ingredient.

7. Use of the hydroxyformamidine compound or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3, for inhibiting production of 20-hydroxyeicosatetraenoic acid.

8. Use of the hydroxyformamidine compound or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3, for the manufacture of a therapeutic agent for kidney diseases, cerebrovascular diseases, or circulatory diseases.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/05108

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D213/74, 401/12, 405/12, 417/12, 409/12, 473/08, A61K31/44, 4439, 4545, 5377, 443, 4436, 4433, 444, 522, A61P13/12, 9/00, 10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D213/00-74, 401/00-12, 405/00-12, 417/00-12, 409/00-12, 473/00-08, A61K31/00-5377, A61P13/00-12, 9/00-10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY (STN), CAPLUS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3998970 A (Stauffer Chemical), 21 December, 1976 (21.12.76), Full text & US 3959368 A	1-6,8
A	US 5646147 A (Hoechst Aktiengesellschaft), 08 July, 1997 (08.07.97), Full text & WO 94/17748 A1 & JP 7-505818 A & EP 638069 A	1-6,8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August, 2001 (21.08.01)	04 September, 2001 (04.09.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/05108

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:

The invention of claim 7 falls under the category of "methods for treatment of the human body by therapy" as provided for in Rule 39.1 (iv) of the Regulations under the PCT as a subject matter of international application which this International Searching Authority is not required to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)